Penile Cancer

Management is based on the finding that cancer metastasises almost exclusively in step-wise fashion from penis – inguinal LNs – pelvic LNs – other. It is extremely rare for vascular metastasis in the absence of palpable LN involvement

Demographics

Incidence 1 in 100,000 population/yr (~ 350 men per year in UK)
Approximately 0.5% of all male cancers; up to 10% in developing countries (India, Brazil, Uganda)
Rates generally falling in all countries ? secondary to improved hygiene
Peak incidence at 50-60yrs

Risk factors

Human papilloma virus (HPV) infection
- HPV 6 and 11 associated with non-dysplastic conditions (warts)
- HPV **16**, **18**, 31 and 33 associated with SCC
- HPV 16 most commonly found subtype
- Overall using PCR HPV seen in ~40% of tumours (Rubin 2001; seen in one third of keratinizing/verrucous tumours and 80-100% of basaloid/warty subtypes)

Phimosis
- Phimosis associated with penile ca in 25-75% of cases – may be higher (2' to destruction of prepuce)
- Carcinogenic effects of smegma suspected though not proven
- Neonatal circumcision protective
  - Risk reduction difficult to quantify (variously reported at 3-10x risk reduction)
  - Some argue that neonatal Cx unnecessary in populations with good hygiene (Frisch 1995 reported a reduction in penile cancer of approx 30% in Denmark without a change in Cx rates – attributed to poverty reduction and improved bathing facilities)

Premalignant lesions of the penis*
- Erythroplasia of Queyrat
- Bowen's disease
- Bowenoid papulosis
- Balanitis Xerotica Obliterans
  - Male lichen sclerosis et atrophicus
  - Typically men in 3rd/4th decade
  - Unknown aetiology
  - Found synchronously with penile cancer in up to 25% of cases
  - Incidence of penile cancer on follow-up between 3-6%.
  - No causal relationship found however
- Condyloma acuminatum
- Cutaneous horn of the penis
- Extramammary Paget's disease
- Leukoplakia
- Pseudoepitheliomatoous micaceous and keratotic balanitis

*NB. Buschke-Lowenstein tumour is a locally aggressive, non-invasive tumour (aka verrucous carcinoma) not premalignant for SCC (although malignant change has been reported with radiotherapy)

Immunosuppression

HIV increases relative risk fourfold (Frisch 2001) – usually associated with concomitant HPV infection

Also increased rates found in patients following renal transplantation (Beserani 2007)

Ultraviolet exposure

Phototherapy with ultraviolet A light (PUVA) believed to be associated with increased risk of penile cancer in pts with genital psoriasis, especially when given with 8-methoxypsoralen. UVB much lower risk

Tobacco

Tobacco products independently associated with the risk of penile cancer formation on multivariate analysis (ie. when phimosis controlled for) - ? promotes dysplastic change in virally loaded cells

Clinical Features

Varied presentation

Typically with lesion or thickening of either the glans or prepuce

Occasionally chronic discharge from phimosis or palpable lymphadenopathy

Rarely pain, bleeding, fistula, retention

Palpable lymph nodes present in 30-60% at presentation – of these half will harbour metastases (node-negative patients harbour micrometastases in approximately 20% of cases)

Overall 20% of patients with inguinal mets will have pelvic mets. Increases to 25-50% in those with two or more nodal mets

Overall 50% 5 year survival:

Negative nodes	66% 5YS
Inguinal nodes	28% 5YS
Pelvic nodes	2% 5YS

NB. 20% of patients with advanced disease have hypercalcaemia, presumably due to PTHrP.

Macroscopy

Invasive penile cancers either papillary or ulcerative. Rates of growth similar but ulcerative more associated with higher stages at presentation

Distribution:			
	Glans	48%	
	Prepuce	21%	
	Glans & prepuce	9%	
	Glans/prepuce/shaft	14%	
	Coronal sulcus	6%	
	Shaft only	<2%	(Burgers 1992)

Microscopic

95% squamous cell cancers. Others include BCC and melanoma. Also mesenchymal tumours (Kaposi's sarcoma, angiosarcoma etc.)

Typically show keratinisation, epithelial pearls and mitoses

Subtypes:

Classic

- Basaloid
- Verrucous
  - Warty carcinoma
  - Verrucous carcinoma
  - Papillary carcinoma
  - Hybrid carcinoma
  - Mixed carcinoma
- Sarcomatoid
- Adenosquamous

Basaloid/sarcomatoid = poor prognosis
Verrucous = good prognosis
Classic = intermediate prognosis

Growth pattern
- Superficial spreading
- Nodular = vertical invasive growth pattern
- Verrucous = exophytic

Broder's grading system for SCC modified for penile cancers. Overall approx 70% low grade cancers. High grade disease correlates well with the likelihood of nodal mets and subsequent survival – low grade disease less well – need for better prognostication. Alternative grading system proposed by Maiche (1991) which is thought to be more accurate for prognosticaion.

Risk factors for nodal mets:
- Stage (particularly corpus cavernosum invasion)
- Depth of invasion
- Grade
- Histological subtype
- Growth pattern
- Vascular invasion
- Lymphatic invasion

NB. Best molecular markers p53 overexpression (Martins 2002) and SCC antigen (Laniado 2003): not independently prognostic however.

Risk factors associated with survival:
- Presence of LN mets
- Number and location of LN mets
- Extracapsular nodal spread

Diagnosis
Diagnostic biopsy mandatory to confirm diagnosis, assess grade, depth of invasion and presence of vascular/lymphatic invasion. Depth assessment and histological analysis can be difficult on Bx; therefore generous, deep biopsy required. Biopsy can only be deferred if there is no doubt about the diagnosis and Mx inguinal nodes is to be postponed until recovery from primary surgery.

FNAC should be performed at the time of diagnostic biopsy in men with palpable nodes. Saisorn (2006) reported the results of FNAC done at diagnostic biopsy in 16 men with 25 palpable nodes. FNAC was done with 20G needle, fixed on slides with 95% alcohol and air dried. Ultrasound guidance not used. Sn/Sp of 93% and 91% respectively, including one false negative and one false positive. All tumours with nodal mets were T2. Suggests that do not need to wait for antibiotic treatment. FNAC accurate enough to guide the need for inguinal dissection. Saisorn's patients went on to have a radical inguinal LND on the ipsilateral side and modified (with frozen section) on the contralateral side.

Penile tumour imaging

Palpation: Surprisingly accurate
Horenblas (1991): accurate in 74% (understaged 10%; overstaged 16%)
Lont (2003): Sn/Sp for corpus cavernosum involvement 86% and 100% respectively

Ultrasound: Small parts 7.5MHz or 10MHz transducer
Cancer hypoechoic
Sensitivity for corpus cavernosum infiltration 100%

MRI: Improved accuracy cf. clinical palpation for T2+ disease
No studies vs. USS
Best results using gadolinium and artificial erection (PGE1) (Scardino 2004)

NB. Clinical examination usually accurate, but for equivocal cases and advanced findings, useful in dictating most appropriate therapy

Lymph node imaging

Palpation: Poor at determining the presence of mets
Only 50% of palpable nodes at presentation harbour cancer
Sn/Sp 90% and 21% respectively (Horenblas 1991)

Ultrasound: Used in conjunction with FNAC
Has been evaluated in patients with palpable and impalpable LNs:
- Palpable: Sn/Sp 93% and 91% (Saisorn 2006)
- Impalpable: Sn/Sp 39% and 100% (Kroon 2005)
  Limited by high false negative rates, reflecting sampling error/failure to identify sentinel node

CT: Limited data
Horenblas (1991) Sn/Sp for inguinal LN mets 39% and 100% respectively. Limited by unacceptable false negative rates

MRI: Few data. One study reporting Sn/Sp of 100% and 97% respectively in patients receiving infusion of iron nanoparticles but no comparison with histology!! (Tabatabaei 2005)
Spacial resolution limited to 2mm

PET: Limited by special resolution of MRI scanner
One study by Scher reported Sn of 89% for inguinal mets (11% false negative rate)

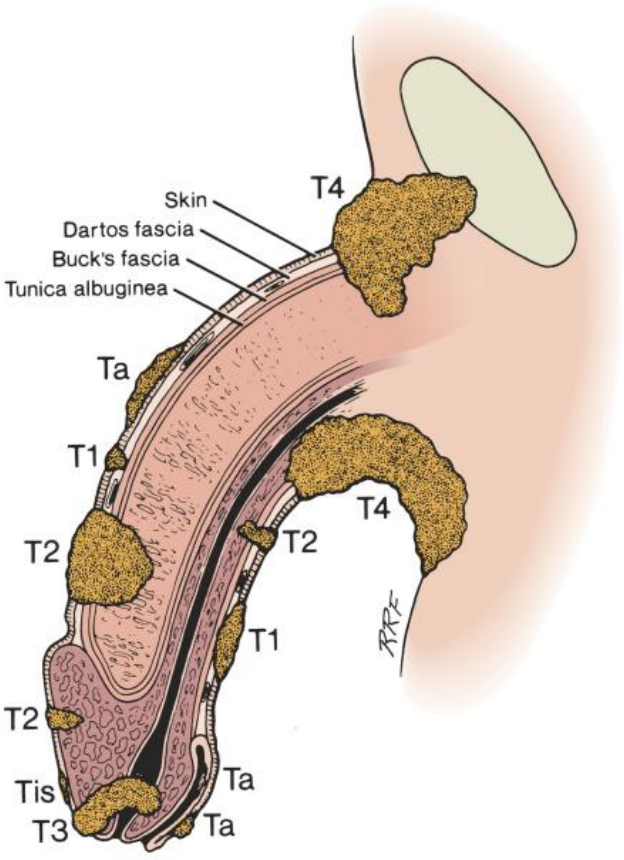
Grading and Staging

Histopathological grading

Gx	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	poorly differentiated/undifferentiated

UICC/TNM Staging

T0 No evidence of tumour
Ta Papillary tumour
Tis Carcinoma in situ
T1 Invasion through lamina propria
  T1a G1/G2 and no lymphovascular invasion
  T1b G3/4 or lymphovascular invasion
T2 Invasion into corpora cavernosa or corpus spongiosum
T3 Invasion of urethra or prostate
T4 Invasion of adjacent structures
N0 Impalpable nodes
N1 Single mobile superficial inguinal LN
N2 Multiple or bilateral mobile superficial inguinal LNs
N3 Fixed inguinal mass or pelvic LN
M0 No mets
M1 Distant mets



Management of the primary tumour

CIS

5% imiquimod cream (Aldara)
5% 5-FU cream (4-6 wk, alternate days)
Laser ablation (Nd:YAG or CO2)
Cryotherapy
Phototherapy
Glans resurfacing and SSG
Often for intractable CIS. Originally described by Bracka. Excellent cosmetic results and long-term outcomes (Hadway 2006)

Ta/T1

Glanular resurfacing (Ta)
Moh's micrographic surgery (Ta/T1a)
Wide local excision (primary closure or SSG) (Ta/T1a)
Glansectomy for T1b

T2

Corpus spongiosum	Glansectomy (with frozen section)
Corpus cavernosum	Partial penectomy (5-10 mm clearance required) Consider radiotherapy*

T3

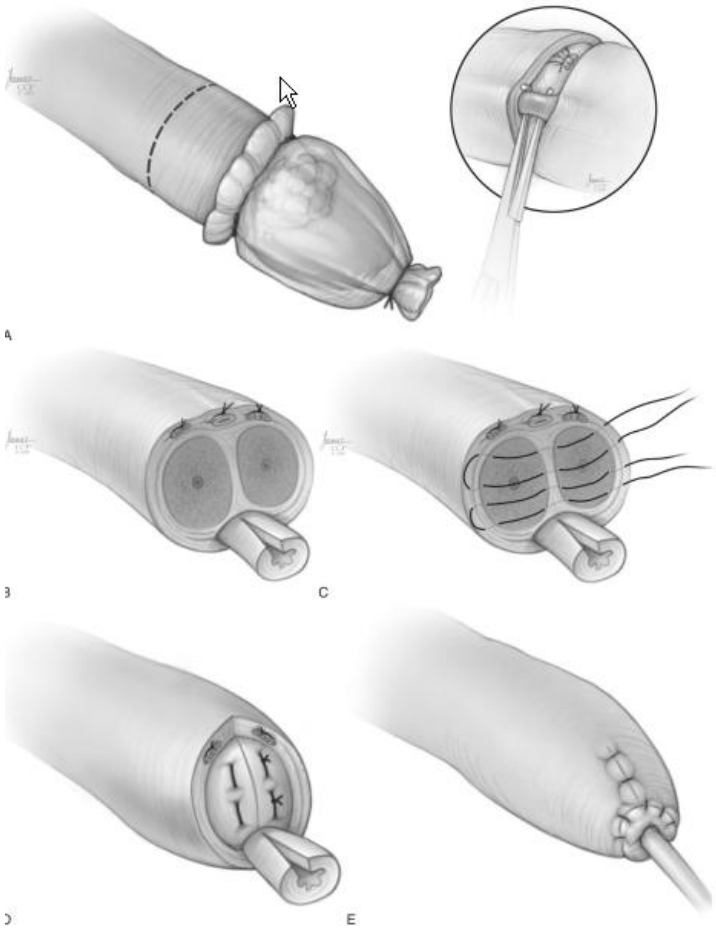
Radical penectomy with spatulated perineal urethrostomy

T4

Consider neoadjuvant chemo and with surgery for responsive disease. Overall response rates to 3 cycles of cisplatin and 5-FU ~70%, causing sufficient downstaging to allow salvage surgery in up to 40% of patients (Culkin 2003). Large defects may require tissue transfer techniques (VRAM or TFL flap)

* Consider brachytherapy for tumours <4cm in men who are sexually active. (70% response, 16% relapse). EBRT has significantly worse outcomes (56% response, 40% relapse) and not recommended. Risks of RT = pain, fistula, meatal stenosis/ urethral stricture (30%), telangiectasia (90%) and necrosis. NB. Salvage surgery not a/w reduced survival cf. primary surgery.

<u>How do you perform a partial penectomy?</u>
Appropriate consent and preparation
Cover penile lesion with condom. Apply tourniquet.
Circumferential (or fish-mouth) incision at level of amputation (~1cm from lesion) through skin and dartos fascia
Open Bucks fascia, ligate and divide neurovascular bundles
Mobilise uretha laterally on both sides.
Incise tunica albuginea on both sides to leave specimen attached via urethra. Close corpora transversely with interrupted 2/0 PDS sutures. Divide urethra, sending proximal shaving for frozen section. Close skin over corporal bodies. Spatulate urethra and attach to skin over urethral catheter. Leave catheter 3-5 days. Risk of recurrence 0 - 8%.



Reconstructive options after penectomy; consider free-radial forearm flap in:

Young fit motivated patients *and*
disease-free for 12 months *and*
favourable histology

Management of patient with impalpable nodes

Dynamic sentinel lymph node biopsy recommended investigation of choice. Limits unnecessary inguinal LND; a/w reduced mordidity and ?improved survival (only reported in abstract form by Pettaway. Remember referral to supra-regional MDT. Risk stratification (EAU guidelines 2004) still recommended in centres without access to dynamic sentinel lymph node biopsy:

Ta, Tis and T1G1	<16.5% risk of micrometastases Surveillance recommended Modified lymphadenectomy for unreliable patients
T1G2 +	Bilateral modified inguinal LN dissection recommended with conversion to full radical inguinal LN dissection in +ve cases.

NB. No role for radiotherapy as prophylaxis:

Efficacy not proven
High morbidity
Difficult follow-up due to fibrosis

Dynamic Sentinel Lymph Node Biopsy (DSNB)

'Sentinel node' first coined by Cabanas in 1977 – described first draining node medial to superficial epigastric vein based on lymphoscintigraphic studies. Removal of nodes from this static location associated with high false negative rates and procedure abandoned
Use of blue dye and radioactive tracer (99m) technetium-labelled nanocolloid to identify sentinel node for excision biopsy. Studies comparing findings of sentinel node to lymphadenectomy specimen give sensitivity ranges from 71% (Spiess J Urol 2007) to 95% (Lietje Eur Urol 2007). **Most studies report false negative rates of ~5%**

NB. A number of reports have shown that DSNB unreliable with palpable or clinically suspicious nodes.

Management of patient with positive nodes

Lymphatic drainage bilateral. Contralateral metastases in 20-30% of cases
Bilateral radical inguinal lymphadenectomy usually performed. However due to high risk of complications some units offer ipsilateral RLND and contralateral modified LND – no evidence for this to date

Radical/modified LND

Inguinal LN: superficial (8-25 nodes) below Scarpa's and above fascia lata. Deep (3-5 nodes) drain superficial nodes thro' fossa ovalis with saphenous vein to join nodes along femoral vein. Most superior leg node is Cloquet's node which join with pelvic nodes
Pelvic nodes: 11-20 nodes along iliac vessels and in obturator fossa

Classic radical LND: Inguinal ligament superiorly, adductor longus medially, Sartorius laterally and femoral vein and artery on floor. Thus includes saphenous vein and fascia lata.

Complication rate approximately 30-50%: oedema, wound infection, wound breakdown, lymphocoele

Modified radical LND: preserve saph. vein + 1-2 cm reduction in lateral and inferior margins. If lymph node positive on frozen section proceed to radical LND. If 2 nodes positive should proceed to pelvic LND (alternatively at second sitting).

No role for radiotherapy for positive lymph nodes. Horenblas (2001) reported that 5 year survival approximately half that of patients treated with surgery (50% vs. 25%).

Development of palpable inguinal lymph nodes during surveillance

Options include immediate bilateral or unilateral LND. Previously stated however that bilaterality expected in up to 30% of cases (Horenblas). Arguments for unilateral LND hinge upon assumption that micrometastases grow at same rate; therefore if after a long disease-free interval bilateral micrometastases should develop synchronously. This assumption based on old literature (Ekstrom 1958) and may be unsound. If ULND performed very

careful surveillance required anyway. An alternative may be unilateral RLND and UMLND/frozen section.

Pelvic lymph node dissection
When single inguinal LN involved risk of positive pelvic nodes <5%
When 2-3 inguinal lymph nodes involved, risk of positive pelvic nodes 23%
When > 3 inguinal lymph nodes involved, risk of positive pelvic LN 56% (Ravi 1993)
Indications:

2 or more positive inguinal nodes.
Positive pelvic nodes on imaging responding to downstaging chemotherapy – performed in concert with bilateral inguinal LND
? Some authors advocate PLND at the same time as inguinal LND as it provides improved staging with little extra morbidity

Pelvic lymphadenectomy includes the external iliac lymphatic chain and ilio-obturator chain. May be open or laparoscopic with the following borders:

- proximal boundary: iliac bifurcation
- lateral boundary: ilio-inguinal nerve
- medial boundary: obturator nerve.

Adjuvant chemotherapy
Less well established role for chemotherapy
Either three courses of cisplatin and 5-FU or vincristine, methotrexate and bleomycin (VMB). VMB a/w 82% 5-year survival in 25 consecutive patients as compared to only 37% in 31 consecutive historical controls treated with radical surgery alone (Pizzocarro 1988). Recommended by EUA for N2/N3 nodes

Advanced/relapsed disease
Surgery not recommended for relapsed disease after LND as prognosis poor and morbidity high. Radiotherapy has no role after LND. Chemotherapy could be considered in patients with good performance status. Cisplatin and 5-FU, or cisplatin, bleomycin and methotrexate used. Results in patients with widespread disease are usually modest, with 32% complete and partial response rate and 12% treatment-related deaths in the most recent study (Kattan 1993). Response rate is similar in patients treated with cisplatin plus 5-FU, but tolerability of this regimen is much better with no treatment-related deaths.

Follow-up
75% of all recurrences in the first 2 years (including all distant recurrences) 90% within 5 years. Therefore more intensive follow-up in the first 2 years with discharge on regular self-examination at 5 years.
Local recurrence in up to 30% patients with penis preserving surgery; 5% for amputations (partial and total). Provided adequate surveillance no impact on overall survival, unlike for patients with regional inguinal recurrences.

	Interval of follow-up		Examinations and investigations	Maximum duration of follow-up	GR
	Years 1 and 2	Years 3, 4 and 5			
Recommendations for follow-up of the primary tumour					
Penile preserving treatment	3 months	6 months	Regular physician or self-examination	5 years	C
Amputation	6 months	1 year	Regular physician or self-examination	5 years	C
Recommendations for follow-up of the inguinal lymph nodes					
'Wait-and-see'	3 months	6 months	Regular physician or self-examination	5 years	C
pN0	6 months	1 year	Regular physician or self-examination Ultrasound with FNAB	5 years	C
pN+	3 months	6 months	Regular physician or self-examination Ultrasound with FNAB	5 years	C

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